2000s

Translational bench-to-bedside research continues to be the hallmark of our Cancer Center. Breakthroughs in research and clinical care is facilitated by two new Cancer Research buildings, and our Center is renamed in honor of philanthropist **Sidney Kimmel**.

Leading in the New Millenium

The Right Treatment to the Right Patient at the Right Time

In 2008, **William G. Nelson**, became the third and current director of the Kimmel Cancer Center.

He has overseen significant expansions in the physical footprint of the Kimmel Cancer Center, moving most cancer care to the outpatient setting and opening satellite locations throughout the National Capital Region. The expansions included the addition of the Skip Viragh Outpatient Cancer Building, the Kimmel Cancer Center at Sibley Memorial Hospital in Washington, D.C., the Johns Hopkins Proton Therapy Center, and the Kimmel Cancer Center at Johns Hopkins Bayview Medical Center. He also added cancer services at Johns Hopkins Health Care & Surgery Center — Green Spring Station in Baltimore County and at Suburban Hospital in Montgomery County.

The treatment of cancer as an outpatient would have been unthinkable when our Center opened its doors in 1977. It is a testament to the progress that has been made over the last 50 years.

"In the future, as cancer evolves further into a disease managed through drug and outpatient treatments, I expect the Center's expanded locations to provide convenient, local treatment instead of requiring people to visit central locations," says Nelson.

The number of people who work for the growing Kimmel Cancer Center and who come to us for treatment has also greatly increased. Today, the Center has 285 full-time faculty, 349 nurses and more than 500 support staff members. There are more than 90,000 patient visits and 9,000 new patients seen across all Kimmel Cancer Center locations in a year.

Nelson also broadened and restructured clinical services and research programs. The Skip Viragh Center for Pancreas Cancer Clinical Research and Patient Care, the Ludwig Center, the Lung Cancer Center of Excellence, the Colorectal Cancer Patient Care and Research Center of Excellence, two Precision Medicine Centers of Excellence, one for prostate cancer and another for pancreatic cancer, the Greenberg Bladder Cancer Institute, the Bloomberg~Kimmel Institute for Cancer Immunotherapy, and the Convergence Institute opened. To address higher death rates among minorities and other underserved populations in Maryland, he established the Community Outreach and Engagement and Diversity and Inclusion in Clinical Research programs.

With emerging discoveries in genetics, epigenetics and immunotherapy showing that cancer cell growth and behavior was less about where it occurred in the body and more about the instruction manual that is contained within cancer and surrounding cells, Nelson reorganized Kimmel Cancer Center research programs to enhance the understanding of how cancer develops, grows and spreads.

NELSON

He integrated studies of specific cancer types into existing programs in cancer genetics and epigenetics, cancer immunology, new drug and drug target development, cancer prevention and control, cancer imaging at the molecular and functional level of cancer cells, and blood cancers and bone marrow transplant. He also added a new program to research cancer invasion and metastasis, aimed at better understanding the leading cause of cancer deaths — the lethal spread of cancer from the place in the body it originated to other tissues and organs.

The restructuring deepened the understanding of the basic biology of cancer within the context of translational — bench-to-bedside — research to develop better prevention, detection and treatment strategies.

"The hope, the ultimate goal, is that we're going to eradicate the ability of cancer to threaten your life and its quality, and ensure that treatment isn't a drag on your life and happiness," says Nelson.

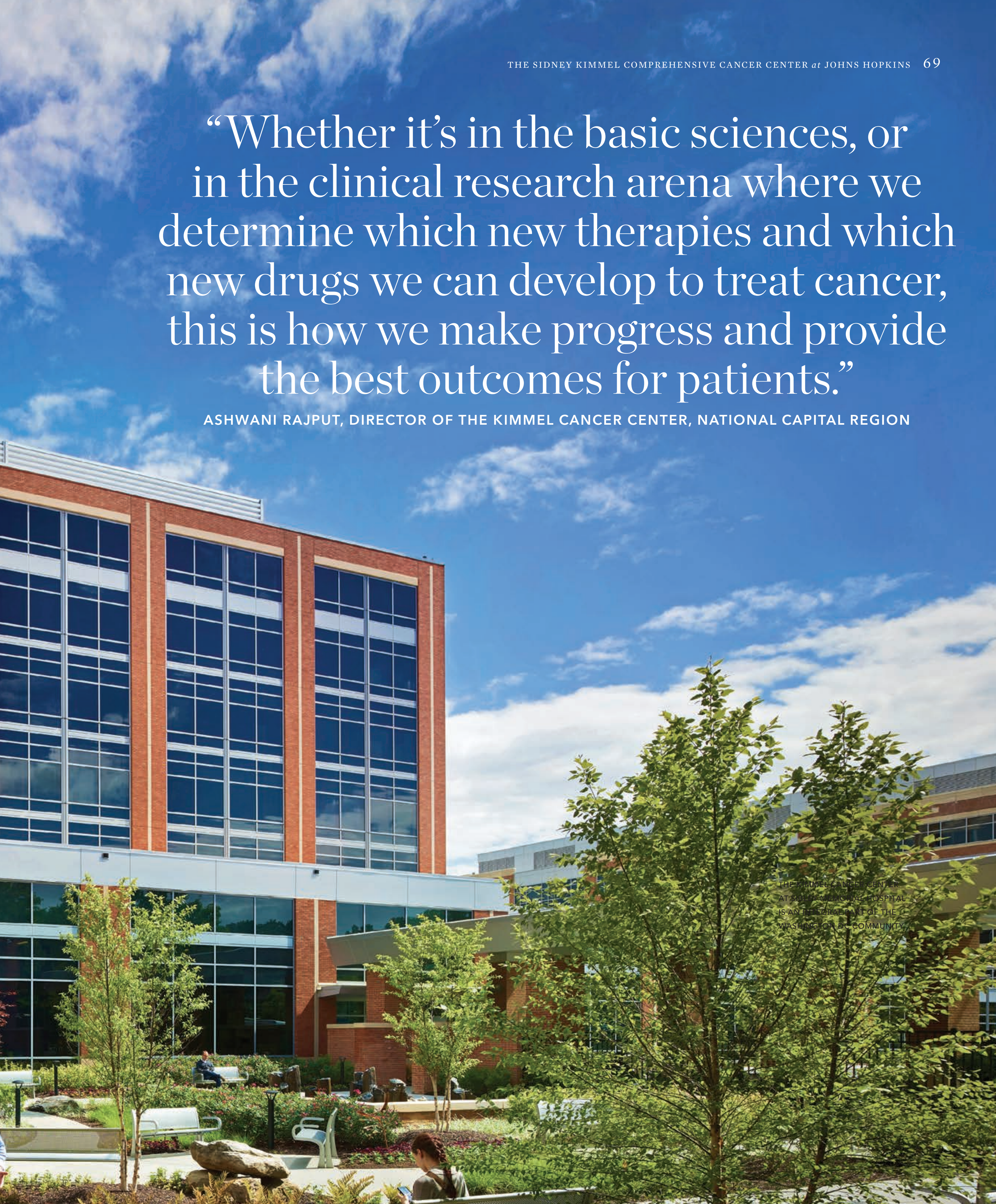
He incorporated the multidisciplinary model — commonly referred to at the Kimmel Cancer Center as the multi-D clinics — into the treatment of all cancer types. The multi-D clinics, pioneered first in prostate cancer and pancreatic cancer, bring together all of the experts involved in treating a patient with cancer to develop the best treatment plan.

"What people need when they hear the words 'I think you have cancer,' is an answer and a plan," says Nelson. "The multidisciplinary clinics bring

THE KIMMEL CANCER CENTER
AT SIBLEY MEMORIAL HOSPITAL

"Whether it's in the basic sciences, or in the clinical research arena where we determine which new therapies and which new drugs we can develop to treat cancer, this is how we make progress and provide the best outcomes for patients."

ASHWANI RAJPUT, DIRECTOR OF THE KIMMEL CANCER CENTER, NATIONAL CAPITAL REGION



THE KIMMEL CANCER CENTER AT SIBLEY MEMORIAL HOSPITAL IS AN INTEGRAL PART OF THE WASHINGTON DC COMMUNITY.

together surgeons, medical oncologists, pathologists, radiation oncologists, nurses — any specialist involved in the treatment of a specific cancer — all working together to the benefit of the patient."

With the shift of most cancer care to the outpatient setting and more cancer therapies coming in pill form, Nelson also proposed a new paradigm for drug discovery to address the high rate of cancer drug failure. To illustrate the problem, he explained that in 2008 alone, the year he became director, there were 750 cancer drugs in clinical trials, with less than 5% of them ever ultimately performing well enough to get approved for cancer treatment.

"Pharmaceutical companies estimate it costs them about $1 billion to discover, develop and get a cancer drug FDA approved. These costs are passed on to people with the disease in the form of high costs for treatments. I believed our Cancer Center could be a part of the solution. We have the drug discovery engine that could help pick the winners from the losers before large sums of money are spent, and we did it," says Nelson. "Kimmel Cancer Center research led to the first FDA approval of a drug across all cancer types based on a specific biomarker that our researchers discovered and then later determined could pinpoint pretty successfully who would respond to a type of immunotherapy drug. We will continue to look for these kinds of opportunities."

Inspired by his own experience at Johns Hopkins, Nelson also gathered together the entire brain trust of Johns Hopkins in the fight against cancer. He refers to himself as "homegrown," as he went to medical school and graduate school at Johns Hopkins and completed his residency and fellowship here.

"I have never delivered any health care of any kind as anything other than a Johns Hopkins physician," he said. "By being around the institution for so long, I've ended up a professor in six departments, and this helps me bring people together across Johns Hopkins. It gave me a good sense of how great we can be when we work together across departments."

Today, under his leadership, the Kimmel Cancer Center spans 35 Johns Hopkins departments and five schools.

The Kimmel Cancer Center represents a broad number of disciplines, with cellular biology, structural biology and DNA research playing roles alongside engineering and computer sciences. Researchers are working to understand how proteins that disrupt cancers can be tucked into drugs and to apply artificial intelligence (AI) tools toward managing cancer gene data — which can number in the billions — speeding research and discoveries, he says.

Nelson also ushered in the era of precision medicine, tailoring research, screening, detection and new therapies to what has been revealed about the unique molecular and cellular characteristics of cancers.

"Our research showed that people carry genetic vulnerabilities that they inherit from their parents, and about 15% of all cancers occur in people who seem to have these genetic predispositions. It doesn't mean they're fated to get cancer, just that they are more susceptible to getting a cancer. What is newer are tests for some of these genes that predict increased risk for cancer among the general populations so that we can use early detection and screening strategies to intervene and diagnose people at the very earliest stage," says Nelson.

This means, he says, that our experts can determine who is not as likely to develop cancer and economize our use of screening tests. In terms of therapy, gene alterations and cancers may predict which treatments will be successful and which will not.

With precision medicine, Nelson set a new direction for the Kimmel Cancer Center, moving it away from a model in which patients are seen for the first time when they experience symptoms and toward one that detects, manages and many times eradicates cancers before patients even know they have them. This new model, he says, preserves health by preventing cancers very accurately, predicting who will get them, and personalizing screening and therapy to each individual.

TWO CANCER RESEARCH BUILDINGS OPEN

The Bunting-Blaustein Cancer Research Building opened in 2000, the first of two new cancer research buildings. Its unique interstitial design allowed building services to be installed and modified without interruption to of research activities on floors above or below. The ten-story, 122 square foot building cost $59 million to build. The Bunting family and Jacob and Hilda Blaustein donated $10 million each toward the construction. It housed programs in cancer biology, hematologic malignancies, urologic oncology, gastrointestinal cancer, pediatric oncology, solid tumor research, including in breast cancer, pharmacology and experimental therapeutics; immunology, and cancer prevention and control.

The David H. Koch Cancer Research Building opened in 2007. The $80 million, 267,000 square foot building, expanded the complex for cancer investigators. New York businessman David Koch donated $20 million toward its construction. With five floors of laboratories and 10 stories of office space, the building is home to researchers of prostate, brain, skin, lung, and head and neck cancers A-250 seat high tech auditorium, named in honor of **Albert H. Owens, Jr.**, the Center's first director, connects research tower to its twin, the Bunting-Blaustein Cancer Research building.

"We are beginning to use our scientific discoveries to determine which treatments and screening interventions will work best for each patient, and just as important, we are using this knowledge to spare patients the risk and adverse effects of treatment and procedures that will not work," says Nelson.

In many ways, the accomplishments and direction of his leadership to date have been guided by his overarching goal to use science to improve the benefits of cancer therapy and reduce its ill effects by "getting the right treatments to the right patients at the right time." This iconic phrase for which Nelson has become known is at the heart of precision (individualized) medicine.

"Over the next decades, the discoveries and developments in treatments will be enhanced by the vast influx of AI-influenced data that will help Kimmel Cancer Center physicians and researchers further tailor treatments on the individual level," he says.

"THE STATE OF THE ART IS JUST THE STARTING POINT OF WHAT WE CAN OFFER. THAT KIND OF TREATMENT OPPORTUNITY – THE LATEST, PLUS SOME – IS WHAT WE HAVE AND ALWAYS WILL DELIVER."

With this long list of accomplishments, it's hard to imagine that Nelson had not set out to become a doctor. He was a soccer standout and chemistry major at Yale University, and planned to study law. A summer job in the laboratory of a cell biologist looking for molecular biomarkers of a rare skin disorder called ichthyosis changed his mind.

"There were clinical trials of some new drugs, and I was in contact with many of the participants. I was struck by how well they understood their disease and their reason for joining the trial. They knew it was an experimental therapy that may not help them, but could help others. That's when I decided I wanted to be a physician," says Nelson.

For most of his career, his research and clinical interests have been focused on prostate cancer.

"When I started in oncology, men were commonly diagnosed at an advanced stage. We had some limited success with treatments, but death rates were far too high," says Nelson. "Since that time, we've gotten PSA (prostate specific antigen), a blood test that made it possible to diagnose men far earlier, so they could benefit from surgery and radiation. We've also developed new treatments. That allowed us to cut prostate cancer death rates almost in half over the last 30 years."

He'd like to see similar progress made against all cancers, and he believes the Kimmel Cancer Center has the talent to make that goal a reality.

"This place is special," says Nelson. "I've been a researcher trying to invent new treatments and take them into the clinic. I've been a clinician working directly with people with cancer. I understand the promise and limitations before us, and I think the time is right to really take some major shots that can transform the cancer problem."

Once of those "shots," he says, has to be in cancer prevention.

"There are about 1.4 million new cases of cancer each year, and this number is expected to increase as our population ages. Cancer is a major health concern, not just in the United States but worldwide. I believe we can prevent people from having some of these devastating diseases," says Nelson. "When we look at screening and early detection that we already do — Pap smear, mammography, colonoscopy, PSA — their use leads to improvements in survival and treatments that are far less deforming and have fewer side effects."

Nelson is also optimistic about laboratory discoveries in prevention that he believes may be able to both stop a cancer from developing and treat cancer. He has stewarded efforts to address behaviors and other underlying causes of cancer, such as chronic inflammation and infection, and directed research and resources to help minorities and other underserved populations that suffer disproportionately higher rates of cancer deaths. Part of this effort includes increasing minority participation in clinical trials.

Building upon the accomplishments of his predecessors, Nelson says the Kimmel Cancer Center remains true to its founding as a place that uses science to improve the care of patients. The labs are no longer physically adjacent to patient rooms, but they remain adjacent in spirit and practice, and this translational research remains at the core of the Kimmel Cancer Center.

"I believe nearly every challenge facing the field of cancer medicine can be solved through translational research," says Nelson.

This expertise in translational research is what makes the Kimmel Cancer Center so special, he says, adding that he wouldn't want to be a director at any other cancer center.

"The major difference at a place like the Kimmel Cancer Center is that the state of the art is just the starting point of what we can offer. That kind of treatment opportunity — the latest, plus some — is what we have and always will deliver," says Nelson. "There is so much we have accomplished here already, but I believe there is much more we can do. This is a great place to be, and the right time to be here. We have tremendous opportunities."

Sidney Kimmel: Helping Others

Historical and transformational giving

"SOMEONE ONCE TOLD me, don't give like it's a pinch; give till it hurts. Extend yourself and give to other people and to good causes." These are the words of philanthropist and Kimmel Cancer Center benefactor **Sidney Kimmel**. In 2001, he made Johns Hopkins history with his $150 million donation — the largest single gift to the university at that time — to support cancer research and patient care.

The Cancer Center was renamed the Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins in his honor.

This historic gift is one of many he has made in support of the Johns Hopkins Kimmel Cancer Center. Since 2001, he has contributed nearly $210 million in total, including $2.4 million to support 12 of our cancer scientists as part of the national Kimmel Scholars Program. Kimmel provided the lead funding for the Hackerman-Patz Patient and Family Pavilion, and subsequently he and Michael Bloomberg provided the lead gifts — contributing $50 million each — to establish the Bloomberg~Kimmel Institute for Cancer Immunotherapy in 2016.

"I am blessed. To be able to support one of the leading institutions in the world and build on its momentum gives so much meaning to what we have all done thus far to defeat cancer and provides even more hope for what can now be accomplished. My goal with this gift is to make meaningful advances in our knowledge of cancer," said Kimmel in 2001.

His efforts in the world of cancer research have changed the face of the disease. He led the charge at the *March: Coming Together to Conquer Cancer* in Washington, D.C., in 1998, which resulted in a doubling of the National Cancer Institute's budget. In addition, he has funded and named cancer centers at Thomas Jefferson University and Memorial Sloan Kettering Cancer Center. Among his most significant achievements in cancer research, Kimmel established the Kimmel Scholars Program, which funded the startup labs of nearly 300 of the nation's most highly regarded researchers, giving birth to the next generation of cancer leadership. He is the recipient of numerous awards, and is the lead individual donor to Stand Up to Cancer, which raises millions annually to fund cancer research.

As a child of the Great Depression, Kimmel remembers the struggles his parents endured providing for the family.

"My sole motive in life was to earn a living. I wanted to be able to help my family," he said.

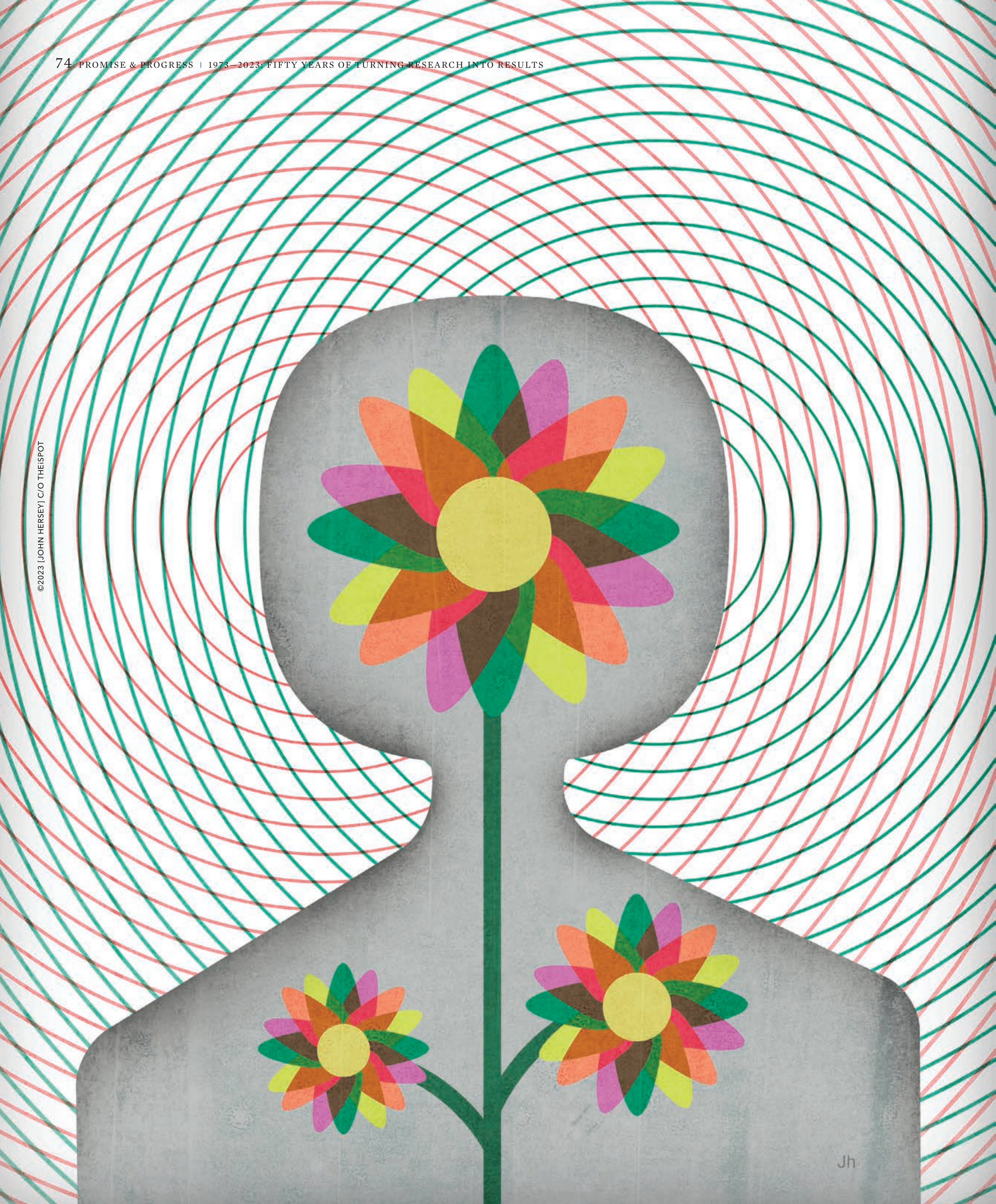
Kimmel, 95, earned his fortune as chairman and CEO of Jones Apparel Group Inc., which he founded in the mid-1970s. The women's clothing manufacturer included such iconic labels as Jones New York, Nine West, Stuart Weitzman and Lauren. His "second career" was in the motion picture industry, where he pursued his love of film. Establishing Sidney Kimmel Entertainment, now SK Global Entertainment, he led the production of more than 75 pictures, which included the highly acclaimed *United 93*, *Hell or High Water* and *Crazy Rich Asians*.

"Sidney Kimmel is one of the great philanthropists of our age. His impact on the field of cancer research is without equal."

He is part of "The Giving Pledge," a commitment by the world's wealthiest individuals to dedicate the majority of their wealth to philanthropy, a commitment that Sidney Kimmel has more than fulfilled already.

Kimmel's philanthropy has reached deep into communities to support the arts, education and medicine, but, above all, his support of cancer research has helped advance the understanding of cancer and bring new and better treatments to patients.

"Sidney Kimmel is one of the great philanthropists of our age," says William Nelson, Kimmel Cancer Center director. "His impact on the field of cancer research is without equal."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Healing Beams

Radiation Oncology has come a long way since its origins as an offshoot of the Department of Radiology and later as a program of the Department of Oncology. Although it didn't receive departmental designation until 2003, the history of excellence in cancer research and patient care and the integral role it has played in the management of cancer have deep roots.

What started 120 years ago with the first radioactive isotopes brought to Johns Hopkins to build a gynecologic brachytherapy program to treat cervical cancer in Baltimore, evolved in the second half of the 20th century to a broad system built around the cancer fighting power of targeted X-ray beams and other radiation therapies. These healing beams are still essential to the care we provide, but since becoming a department 20 years ago, it has grown into much more. Molecular radiation sciences, knifeless radiosurgery, proton therapy, radiopharmaceuticals, radiosensitizers, nanoparticles, targeted and immune stimulating therapies, large database-driven clinical informatics, informatic systems, efficiency models, and inventions that propel research and make the clinical care safer are now part of our 21st century cancer science and medicine.

Building upon the strength and the work of early pioneers, Radiation Oncology and Molecular Radiation Sciences experts have earned recognition as world leaders in developing transformational concepts and translating basic developments into novel therapies that have changed the standard of care and improved the lives of patients with cancer.


VISWANATHAN

"Caring about our patients is our top priority," says **Akila Viswanathan**, Director of the Department of Radiation Oncology and Molecular Radiation Sciences. "Combining advanced technology with compassionate care is the hallmark of Johns Hopkins Medicine. Innovations beyond standard technology set us apart from a routine experience."

BOLD GROWTH

Radiation Oncology started with a small team working in the basement of the Halstead Building as they awaited the opening of the Cancer Center in 1977. Computer technology was limited as were the machines that delivered radiation to patients.

Stanley Order, who was director of the Division of Radiation Oncology from 1975-1990, and **Moody Wharam**, director from 1990-2000, were the first two faculty members in Radiation Oncology. The existing radiation-delivering machinery had not caught up with the forward thinking ideas of the Cancer Center's early radiation oncology pioneers, and Order and Wharam worked together to get the equipment up to date. They converted two antiquated cobalts, treatment machines no longer in use today that produced a beam of gamma rays from a cobalt isotope, to five linear accelerators, which use targeted, high energy X-rays. They also added a cobalt unit and two simulators.

The Radiation Oncology Department at Johns Hopkins was among the first in the nation to break off from the Department of Radiology and Radiological Sciences to join forces with the Department of Oncology to tackle the cancer epidemic that had warranted a national war against cancer. Johns Hopkins was home to one of just a handful of strong academic programs in radiation oncology.

When the Center opened in 1977, it had all the latest technology and equipment available at the time. It also had more cancer patients than the physical space could accommodate. The radiation oncology clinic had to expand to twice its original size to accommodate the growing patient load.

"COMBINING ADVANCED TECHNOLOGY WITH COMPASSIONATE CARE IS THE HALLMARK OF JOHNS HOPKINS MEDICINE. INNOVATIONS BEYOND STANDARD TECHNOLOGY SET US APART FROM A ROUTINE EXPERIENCE."

Years later, there were two additional expansions, one with the opening of the Kimmel cancer Center's Harry and Jeanette Weinberg building and another with the satellite facility at Greenspring Station. Additional facilities were again added at Suburban hospital in Montgomery County and Johns Hopkins Sibley Memorial Hospital in Washington, D.C., which would later become home to the proton therapy center.

PIONEERING DISCOVERIES

Strong leadership has helped pave the way for pioneering discoveries. Order developed radiolabeled antibodies to treat liver cancer. He was also ahead of his time, developing a version of telemedicine. In 1989, the Cancer Center developed collaborative radiation oncology services with St. Agnes Hospital in Baltimore and Chambersburg Hospital in Chambersburg, PA.

Patient information from Chambersburg, such as X-rays and charts, was relayed to the Cancer Center via computer, fax, and video telephone hook-up. A telephone conference brought physicians from all of the hospitals together for case review.

Wharam, who specialized in pediatric oncology, was also a pioneer. When our Center opened, just 50% of children diagnosed with cancer survived. The National Cancer Institute appointed four study groups to investigate common childhood cancers, and Wharam received the unusual distinction of being named to two of these groups. From 1980 to 1990, he served as director of the radiation oncology committee of the pediatric oncology group, a U.S. and Canadian collaborative group that studied childhood cancers. His roles in these premier groups made him an active participant in all of the pivotal pediatric cancer research at the time. it was research which led to dramatic increases in pediatric cancer survival rates. The four separate groups have since merged into one known as the Children's Oncology Group.

Wharam, who passed away in 2018, was part of another first, when he collaborated with pediatric oncologist Bridget Leventhal in a groundbreaking 1980s study of treatment reduction in Hodgkin's lymphoma to prevent harmful toxicities. Their research led to refinements in therapy that allowed certain patients to receive less radiation or forgo it altogether without an increased risk of recurrence.

He also developed the standard of care for rhabdomyosarcoma, a childhood cancer of the connective tissue that attaches muscles to bones, combining chemotherapy and radiation therapy, a treatment so effective it remains the standard today.

In the early 1990s, years before advanced radiosurgery equipment had been developed, he innovated a way to deliver radiation very precisely to preserve vision for a toddler diagnosed with cancer in both eyes.

Wharam's pioneering influence earned the department the distinction as one of just a select few in the nation with expertise in treating pediatric patients, and this was instrumental in helping the department gain approval for a proton therapy center, which includes a specialized pediatric team.

"Our program grew into the best one in the country. We have first class scientists and clinicians and the finest physicists, residents, nurses, radiation therapists, and dosimetrist in the business," said Wharam.

Theodore DeWeese, now Interim Dean of the Johns Hopkins School of Medicine, was named the first Director of the Department of Radiation Oncology and Molecular Radiation Sciences.

DeWeese, a prostate cancer expert, collaborated with researcher Shawn Lupold, to develop aptamers, small molecules that work like antibodies to target unwanted things in our bodies, like cancer. The aptamers deliver silencing RNAs specifically into cancer cells to render cancer cells vulnerable to the DNA damage caused by radiation therapy while protecting normal cells.

DeWeese was instrumental to bringing proton therapy to the Kimmel Cancer Center and advancing radiation oncology research, recruiting **Marikki Laiho** to head Molecular Radiation Sciences and inventor **John Wong** as Chief Physicist.

AN INVENTOR

"Radiation oncology requires the right balance of technology development, laboratory research and dissemination of knowledge for clinical decisions," said Wong, now retired.

He was the inventor of many key instruments used in radiation oncology treatment and the research of cancer.

Among his inventions are the ABC interactive device that coordinates breathing with radiation treatment. As patients breathe, tumors move, and ABC locks the breath in place for short, comfortable periods to make sure the radiation hits its cancer target.

ABC has been enhanced with 4D CT and MRI imaging. Radiation oncologist and lung and esophageal cancer expert **Russell Hales** explains that the fourth dimension is the capture of movement. The 4D imaging captures a few seconds of patient's breathing, and these data are used to predict how and where the tumor will move throughout treatment.

Hales is conducting the critical research to validate the ability of image-based technologies to predict tumor movement during radiation treatment.

"We are one of the few places that are doing this kind of research," says Hales. When completed he says the research should produce the most accurate measurement of tumor movement."

Wong was also the inventor of cone-beam computed tomography, which has become an integral part of radiation oncology treatment and research. CT imaging delivers clear images of bone, soft tissue, and tumor, making it a desirable guidance system for radiation treatment.

The Raven quality assurance device, which connects to machines and quickly performs a series of measurements to ensure they are functioning correctly, and the CT couch, which integrates image guidance with treatment delivery, are also among Wong's inventions.

Another one, called the Small Animal Radiation Research Platform (SARRP), gave researchers the ability to study human therapies in animal models before they are taken to the clinic and was essential to developing more effective and safer therapies. SARRP is a downsized version of a human machine, allowing researchers to perform human-quality radiation delivery in animal models.

DEWEESE

"In radiation oncology, we don't have the means to study mechanisms in a living animal subject, and this machine helps us do that," said Wong.

WONG

MOLECULAR RADIATION SCIENCES

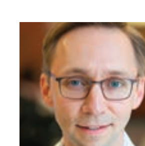
"When we think about radiation therapy, it is high technology, but the complexity of cancer requires that we have a better understanding of the biology," says Marikki Laiho, Director of Molecular Radiation Sciences and Willard and Lillian Hackerman Professor of Radiation Oncology.

LAIHO

The work of Laiho and molecular radiation sciences researchers is aimed at better understanding the mechanisms cancer cells use to survive radiation therapies. They are looking for kinks in cancer cells' armor that can be exploited to prevent them from sensing and repairing the DNA damage caused by radiation therapy.

"DNA damage is not unique, but our research focus is," says Laiho. "There is not a radiation and molecular radiation sciences research program anywhere with the depth and focus we have here."

Among the research projects are studies of cell repair molecules known as PARPs. Drugs called PARP inhibitors can sensitize cancers to radiation therapy and stop cancer cells from making repairs after therapy.



HALES

Understanding the signaling pathways involved in DNA damage, and in particular the role they play in deadly glioblastoma brain cancer is another area of study. Researchers are investigating the relationship between DNA and its marking by epigenetic tags and how they contribute to cancer cell development and survival. Although each has been studied individually, Molecular Radiation Sciences researchers were among the first to explore how they work together in cancer.

Researchers also want to figure out why some tumors respond to radiation therapies and chemotherapies while others do not. Using genetic tools created to selectively introduce cancer mutations into tumor cells, researchers can explore and observe how the cells respond to cancer therapies and devise strategies to combat treatment resistance.

Heat increases the sensitivity of cancers cells to radiation therapy, and another approach uses magnetic nanoparticles that generate heat when exposed to magnetic fields. Sensitizing cancer cells with heat, could make it possible to lower radiation doses or treat cancers that would be otherwise unresponsive.

Testosterone, a hormone that prostate cancer cells need to survive can also play a role in its demise. Researchers believe testosterone causes breaks in the DNA that could make cancer cells more vulnerable to treatment with radiation therapy. Short pulses of testosterone—enough to stimulate the brakes but not too much to stimulate the cancer—followed by radiation therapy to cause even more DNA breaks, can overwhelm and kill prostate cancers.

A biodegradable hydrogel with the consistency of toothpaste could help protect vital organs from damage during radiation therapy. The hydrogel separates the tumor from organs by about a finger's width, and this extra space allows the radiation to fall off and protect surrounding tissue and organs. Hydrogel spacers are most commonly used in the treatment of prostate cancer, but they are being studied in pancreatic cancer, liver cancer, gynecologic cancers, and head and neck cancers.

Laiho's own research project is focused on a cellular machinery, called POL1, that cancer needs to survive. POL1, she says, is necessary for cancer cells to maintain their rapid growth. In her laboratory studies using human cells, new small molecule inhibitors break down this critical activity. The next step is clinical trials.


McNUTT

ONCOSPACE

Radiation Oncology researchers led the way in applying technology to precision medicine—treatments tailored to the unique aspects of each patient's cancer.

Physicist **Todd McNutt** developed a computerized data mining system called Oncospace that analyzes data from prior patients who received radiation therapy to improve the treatment of new patients. It sorts through all of the data on cancer patients treated at the Kimmel Cancer Center, taking into account and connecting all of the variables: age, underlying health conditions and other treatments patients are receiving and figures out how all of these variables relate and influence toxicity and response to treatment. It evaluates the therapies that worked best for a particular cancer—as well as those that resulted in less than favorable outcomes —and generates an optimal treatment plan.

"The practice of cancer medicine naturally creates data," says McNutt, "but for the first time in history we have the technology to sift and sort through this data in completely new ways."

The success of precision, individualized medicine, including the ability to determine which patients will benefit from a particular drug or treatment and which ones will not, rested on the ability to conquer big data. Oncospace was one of the first practical demonstrations of this promise.

"Todd has proven that large data warehouses of patient information collected from previously treated patients can be used to individualize treatment decisions for new patients," said Ted DeWeese, Interim Dean of the Johns Hopkins University School of Medicine and former Director of the Department of Radiation Oncology and Molecular Radiation Sciences.

Oncospace does more than collect and store data. It takes informatics to the critical next level with the capability to perform interactive analysis that informs clinical decision making. Radiation oncologist and head neck cancer expert **Harry Quon** provided the crucial link to put the system to test in the clinical practice.

"I could tell you very accurately where the radiation dose goes," says McNutt, "The important question in treating patients is where should it go and where shouldn't it go."

Head and neck cancer patients were the ideal choice for testing Oncospace in the clinical setting because they are among the most difficult cancers for radiation physicists and oncologists to plan. They often require 20 treatment revisions as they work to design a treatment plan that hits the cancer without causing damage to vital organs and glands, such as the voice box and salivary glands.

"We can build predictive models of toxicities and other side effects based on data we have collected from prior patients. including indicators that a patient may be at higher risk for certain treatment toxicities and use this information to adjust the treatment plan," says McNutt.

More recently, they have begun incorporating data on disease response: Is the cancer stable? Has it progressed? Did it recur? Imaging used for treatment simulation are also being incorporated into the collected data to track the history of a tumor throughout treatment. It could help tell early on in the treatment of a cancer if a tumor is responding or if a change to the treatment plan may be necessary.

McNutt says this latest variation is the radiation oncology version of the work being done in cancer genetics and molecular biology using genetic biomarkers to track and monitor the response of cancers to drug therapies.

"It's real time, in-treatment monitoring" says McNutt. "The same way we use the system to relate the dose of radiation to the salivary gland to the loss of gland function we can use it to relate treatment plans to treatment responses."

The success in head and neck cancer has led to Oncospace now being applied to a variety of cancers, including lung, pancreatic, and prostate cancers.

RADIOSURGERY

Stereotactic body radiosurgery (SBRT) is an option for some cancer patients who have tumors that cannot be removed through traditional surgery. This treatment, sometimes referred to as knifeless surgery, uses high but super-focused doses of radiation to destroy tumors while also limiting side effects to nearby normal organs and tissue.

When pancreatic cancer SBRT is performed, tiny gold seeds, about the size of a grain of rice, are inserted by needle into the pancreatic tumor. They serve as reference points to help guide the radiation oncologist as they treat the cancer. Using the same needle that places the seeds, radiation oncologists removed tiny pieces of the tumor for genetic sequencing.

This unique research study proved that tumors could be sequenced through this small sampling of cells, and the genetic information could be used to individualize treatment in patients with inoperable pancreatic cancer.

"We were the first ones to try this, and we proved it could be done," said **Joseph Herman**, former radiation oncology faculty member who led the initial study.

Stereotactic radiosurgery is also being used by **Amol Narang** to get more pancreatic cancer patients to surgery. Building upon earlier research, he is using SBRT in pancreatic tumors that have attached to nearby blood vessels, making surgical removal of the entire tumor difficult or impossible.

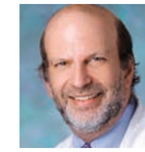
Combining chemotherapy with radiosurgery in these cases helps shrink tumors away from the blood vessels, making surgical removal of the tumor possible for more patients. The immune priming ability of radiosurgery is also being studied in clinical trials of pancreatic cancer patients.

The prevailing opinion in cancer research was that chemotherapy and radiation therapy suppressed the immune system, but Kimmel Cancer Center radiation oncologists proved that may not be the case.

Focused radiation, like what is used in stereotactic radiosurgery, they found may actually stimulate an immune response. Collaborating with Kimmel Cancer Center cancer immunology experts, radiation oncology experts used the small animal radiation research platform to study a combination of radiosurgery and an immune therapy drug in animal models.

Radiation therapy is considered a localized treatment but when combined with immune therapy, it gains an added systemic activity. Immune therapy prevents cancer cells from deploying immune dampening regulatory cells, and with the regulatory cells taken care of, they could use radiosurgery to enlist the entire complement of immune cells to fight the cancer. Killer T cells that, as the name implies, kill cancer cells, memory T cells that remember the tumor cells and have the power to keep the cancer in check indefinitely, and B cells which generate antitumor antibodies that interfere with the cancer cells DNA and stop them from replicating new copies.

This initial study was led by former radiation oncology resident **Andrew Sharabi** and former Bloomberg~Kimmel Institute for Cancer Immunotherapy researcher **Charles Drake**. Sharabi's research was selected from thousands of submissions as a featured presentation at the 2014 annual meeting of the American Society of Radiation Oncology. It was the first basic science research to be highlighted at the meeting in over a decade.



KLEINBERG

For brain tumor expert **Lawrence Kleinberg**, SBRT means he can safely treat the spread of cancer in the brain.

"Before we had radiosurgery, we had to treat the entire brain with radiation and that, of course, caused many side effects, said Kleinberg. "Now, in most situations, we can treat very small areas of the brain with almost no side effects."

As a result, the Kimmel Cancer Center radiosurgery team offer one of the few treatment options for patients with spread of cancer to the brain.

BRACHYTHERAPY

Brachytherapy is a widely used and promising tool of radiation therapy and commonly used in the treatment of prostate cancer and gynecologic cancers as an alternative to surgery.

NARANG

In prostate cancer, radiation is delivered to the prostate via tiny seeds about the size of a grain of rice. Accurate placement of these seeds has been the biggest challenge, but brachytherapy expert **Danny Song** has been a leader in pioneering guidance systems that ensure the seeds are deployed correctly.

SONG

To destroy prostate cancer, about 50 to 100 seeds are placed by needle in the prostate while the patient is under general anesthesia. The greatest limitation to brachytherapy, Song says, was that there was no good real time way to see if the seeds were getting to the correct place. X-ray showed the seeds but did not provide a clear image of the prostate, and ultrasound shows the prostate well but not the seeds.

He decided to combine the two technologies into one. In a collaboration with Johns Hopkins University engineers, Song developed RadVision. As seeds are placed, multiple X-rays are taken and fed into a computer to generate a three-dimensional arrangement of seeds. The seed positions are then superimposed over ultrasound images to ensure the right number of seeds has been placed and to guide the placement of additional seeds, if needed.

RadVision received FDA approval after a clinical study that proved it provided the most accurate seed placement. Patients who have received brachytherapy often also require external beam radiation to compensate for an inadequate seed placement, but Song says seed placement with RadVision is so accurate it may eliminate the need for additional radiation treatments.

KUMAR

In addition, a high dose rate prostate brachytherapy program was launched at the Kimmel Cancer Center at Sibley Memorial Hospital in 2023 under the direction of **Rachit Kumar**.

In gynecologic cancers, Akila Viswanathan, Director of the Department of Radiation Oncology and Molecular Radiation Sciences, was the first in the U.S. to use real time magnetic resonance (MR)-guided interstitial brachytherapy for the treatment of gynecologic cancers.

Using active magnetic resonance imaging guidance, physicians insert several hollow catheters into the tumor. Tiny, radioactive seeds, tethered together by a long thread are inserted into catheters and remain there for about 10 minutes, providing a rapid but high dose of radiation to control cancer cells. A computer controls the insertion and removal of the seeds, ensuring a precise dose throughout the tumor.

"Gynecologic cancers can grow very fast and require very focused high dose to attack the tumor," Viswanathan explains.


MEYER

The entire outpatient procedure takes just a few hours and provides a lifetime of benefits to patients.

"I wanted women who have inoperable cancer that is limited to the gynecologic area to be cured of this cancer," she says.


WRIGHT

Women who have surgery for cancer often lose their entire gynecologic tract, including the cervix, she explains. Brachytherapy preserves these organs, which is particularly important for young women.

The types of MR technology she uses are unique. Working with the team of physicists who write special codes to direct the MRI scanner, she can look inside a tumor and provide a variety of details not available with traditional MRI. Outcomes are excellent for cervical cancer and recurrent uterine vulvar and vaginal cancers, Viswanathan says, with published data showing MR-guided brachytherapy survival rates of over 90%. As a result, Viswanathan is in demand, seeing about 300 patients a year from all over the world. She is training other radiation oncologists to perform the procedure, which she recently expanded to the Kimmel Cancer Center at Sibley Memorial Hospital.


POMPER

THERANOSTICS

A new approach dubbed "theranostics," because it combines the diagnostic properties of molecular imaging with cancer therapy was developed at the Kimmel Cancer Center.


BHUJWALLA

Led by imaging experts **Martin Pomper** and **Zaver Bhujwalla**, and radiation oncologist **Ana Kiess**, the novel approach takes advantage of important molecular components of cancer and allows researchers and clinicians to see inside the cancer cell and view them as they are being treated.


KIESS

The team developed ultra-tiny structures called nanoparticles filled with a drug that kills cancer cells and sensitizes them to radiation and a radiopharmaceutical or cell imaging agent. The nanoparticle is targeted to PSMA, which is present at high levels in prostate cancer, so that it zeroes in on and delivers its anticancer payload specifically to prostate tumors. The particle is labeled with a radioactive isotope which can be imaged or used to treat cancer. It is given intravenously so that it can attack cells growing anywhere in the body.

Kiess and Pomper worked with chemists to modify a drug called LU-PSMA-12, to make it specific to cancer cells and less likely to go into normal cells. The drug is being studied in multicenter clinical trials of advanced prostate cancer.

LESS IS MORE

The ability to shorten the several week course of radiation therapy is a new area of research Radiation oncologist and colorectal cancer specialist **Jeffrey Meyer** is studying—whether abbreviating a typical five-week course of radiation therapy to five days, followed by chemotherapy two months later and then surgery. The regimen is easier for patients, with far less interruptions to their normal routines.

In early studies, long-term outcomes appear to be as good as the traditional, longer courses of radiation therapy, Dr. Meyer says, but adds that the research continues.

Jean Wright, Director of the Breast Cancer Program's Radiation Oncology service, is studying a similar approach for breast cancer.

In the 2000s radiation therapy was delivered over five to seven weeks for almost all patients needing breast radiation, Wright says. About 15 years ago, studies found that shorter, three to four week courses were as effective for patients at lower risk for breast cancer recurrence, and, she says, they have moved to these shorter courses for many patients.

She is also exploring the benefits of an even shorter, one-week, high-dose whole breast radiation approach. The very convenient course has to be weighted for each patient, depending on their breast cancer risk as well as personal preferences and priorities, Wright says.

"This is another great example of how our field is evolving toward patient-centric, tailored treatments," says Wright.

PROTON THERAPY

Proton therapy uses charged particles, rather than photon therapies' high-powered X-rays beams, to kill cancer. Proton does not replace photon radiation therapy but is another important tool our experts have to treat cancer.

The Johns Hopkins Proton Therapy Center opened in 2019 at Johns Hopkins Sibley Memorial Hospital. It is one of only about 40 centers in the U.S. and one of a few with dedicated proton beams for research and a specialized pediatric team.

The Proton Therapy Center is one of the most comprehensive in the world with technology to deliver the most advanced and patient-centered care. It combines cancer treatment excellence across all disciplines with proton therapy excellence, building upon a lengthy history and strong foundation of pioneering discoveries in radiation therapy.

See section 6, page 128 to read more about the Johns Hopkins Proton Therapy Center.

MILESTONES IN RADIATION ONCOLOGY AND MOLECULAR RADIATION SCIENCES

1973: **Stanley Order** is appointed director of the Division of Radiation Oncology for the newly approved comprehensive cancer center at Johns Hopkins

1985: Radiolabeled antibodies prove effective against liver cancer

1990: World-renowned pediatric radiation oncologist, **Moody Wharam**, is appointed director of Division of Radiation Oncology

2003: Department of Radiation Oncology and Molecular Radiation Sciences is established, with **Theodore DeWeese** as director

Molecular Radiation Sciences division established

2004: **John Wong** is named chief of physics, bringing with him his earlier inventions of cone beam CT and his small-animal radiation research platform

2007: The stereotactic body radiation surgery program begins, knifeless surgery that uses focused beams of radiation to kill tumors

Marikki Laiho recruited to direct Molecular Radiation Sciences division

2008: Molecular radiation sciences research deciphers the biology of DNA damage response to radiation therapy and how cells sense and repair this damage

CT-guided miniature versions of the equipment used to treat patients are invented and used to perform first-of-its-kind research, allowing scientists to study the best ways to target radiation-based treatments to tumors and at the same time prevent damage to normal cells

Early gene editing method demonstrates how Chk1, a prototypical therapeutic target, functions in normal cell growth and in cells under stress

2009: A computer-assisted version of brachytherapy, a prostate cancer therapy that uses radioactive seeds inserted into the prostate to kill cancer cells, is developed, allowing for more precise placement of seeds

Molecular Radiation Sciences hosts first symposium on DNA damage repair

Magnetic hyperthermia program established, directed by **Robert Ivkov**, to exploit magnetic nanoparticles for cancer hyperthermia in alternating magnetic fields

2010: Oncospace, a computerized data-mining system, analyzes data from prior patients to improve the treatment of new patients

Human prostate tissues cultured in dish to investigate response to DNA damage

The Johns Hopkins Kimmel Cancer Center at Sibley Memorial Hospital opens, and includes radiation oncology services

2011: RNA aptamers developed to block DNA repair as a method to augment radiation response

2012: A drug that protects radiosensitive mice from low-dose-rate radiation identified

2013: Small animal radiation research platform used for targeted radiation delivery to glioblastoma to investigate new combined treatment strategies with immune checkpoint inhibitors

2014: Novel inhibitors of RNA Pol I, necessary for cancer growth, identified as a potential anticancer strategy

Discovery of new pathway by which p53 suppresses tumor development

First FDA-approved, real-time prostate cancer brachytherapy treatment, planning and guidance system implemented

2015: The Kimmel Cancer Center partners with United Medical Center and Howard University to bring cancer care to the most underserved communities in Washington, D.C.

Magnetic hyperthermia enhances therapeutic response to radiation in mouse prostate cancer models

2016: **Akila Viswanathan** is appointed director of the Department of Radiation Oncology and Molecular Radiation Sciences, and brings her pioneering therapies using CT- and MRI-guided brachytherapy to the treatment of cervical and other gynecological cancers

Minibrains grown in dish to aid research and individualized therapy

2019: The first phase of the Johns Hopkins Proton Therapy Center opens, with phases two and three opening in 2020

2021: First canine clinical trial using magnetic nanoparticles initiated

2022: **Xun Jia** is appointed chief of medical physics division in radiation oncology

2023: Palliative care program launches, managed by **Annie LaVigne**

Kimmel Cancer Center radiation oncology program at Sibley Memorial Hospital builds high dose rate prostate brachytherapy program

Pluvicto treatment program launches following several radiopharmaceutical trials

A Model Clinic

AT MOST HOSPITALS around the country, diagnosis and treatment revolved around the care team, with a series of visits with medical, surgical, and radiation oncologists and other specialists at different locations. Numerous appointments for tests, care decisions, and treatments were spread out over time. At the Kimmel Cancer Center, our experts followed an opposing model in which the care team revolved around the patient in one central location.

The Johns Hopkins Multidisciplinary Clinics—the MultiDs as they are known—were born out of the desire for the Center's clinical programs to match the strength of its basic science research programs. They have played a vital role in improving the treatment of difficult cancers, such as pancreatic, liver, lung cancers, and more.

"I can't think of another place like this, with this level of interaction," says **Bert Vogelstein**, Clayton Professor of Oncology and Co-Director of Ludwig Center for Molecular therapeutics, whose genetic discoveries were and example of the basic science woven throughout the Multi-Ds, informing and improving cancer diagnostics and treatment. "You can't manufacture that kind of environment. It has to be built from the ground up, and we're very fortunate to have it here."

Our experts envisioned a clinic in which patients could come to the Kimmel Cancer Center, and after a single day's visit, receive an integrated treatment plan representing the multispecialty expertise of all experts involved in the treatment of each cancer type. The multidisciplinary care model ensured that every expert involved in the treatment of a particular cancer literally has a seat at the table when recommending a treatment plan to the patient. The clinic seamlessly incorporated all elements of cancer care, including diagnosis, therapy, follow up care and surveillance, palliative medicine, and survivorship.


FELICIANO

"We're not just discussing the treatments that patients will need for their particular cancer but what other resources we will need to enlist for each patient based on what we know about them, their medical history, social history, and their life circumstances, because treatment isn't just about the cancer itself," says **Joy Feliciano,** thoracic cancer expert and Cancer Diagnostic Clinic Medical Director. "It's about how this patient might need rides to chemo or that one might need us to coordinate care with their cardiologist because they have a pacemaker."

The clinics marked a major step forward from the early days of the Center when cancer care was often a singular approach. If a tumor could be removed with surgery, the patient was treated first by a surgeon and handed off to medical and radiation oncologists for chemotherapy and radiation therapy.

A radiologist would image the tumor and send a report to the oncologist. All of the experts would perform their tasks well, but there was no concerted effort.

"Cancer therapy transcends the boundaries of medical and surgical disciplines, so it was important to have all of the key players involved in the plan and execution of therapy from the onset," says **Elizabeth Jaffee**, Deputy Director of the Kimmel Cancer Center and co-director of the Skip Viragh Center for Pancreas Cancer Clinical Research and Patient Care. "By the end of their visit they have received a rapid, wholistic treatment plan, including available clinical trials of the most novel new therapies."

This single-day approach is highly unusual in cancer care, says **Russell Hales,** radiation oncologist and Director of the Thoracic Oncology Multidisciplinary Clinic. His research has helped prove its benefits.

Although he knew patients liked the Multi-Ds, he wanted to be sure, by examining objective data, that it was the best approach for them. In 2017, he compared outcomes of lung cancer patients who received care through the Multidisciplinary Clinic with patients who received their care outside of the Clinic with individual providers through a more traditional care model.

Their findings showed that one year survival at the clinic was 82% compared with 64% for patients treated outside the clinic. The next year, Kimmel Cancer Center radiation oncologist **Ranh Voong** presented additional findings showing that the clinic provides a costs savings of 30% over traditional care, presumably because patients receive more streamlined planning and treatment, avoiding unnecessary appointments and tests.

"You don't see this magnitude of improvement in some of the newer drugs coming out, and it's even more significant because patients in the healthcare system are saving money," says Hales.

The Kimmel Cancer Center has a Multidisciplinary clinic for every cancer type.

Patients travel from around the country, across the U.S., and throughout the state and region.

"This kind of care is in the DNA of the Kimmel Cancer Center," says its Director **William Nelson**. "The collaboration across disciplines is part of our history and it continues today. We never forget the science, and that puts us at the forefront of clinical breakthroughs."


WOLFF


HOLDHOLF


VOONG


LAHERU


SHARFMAN

A snapshot of our many specialty centers and clinics emerging from this multidisciplinary model of care and the generosity of donors who make them possible:

Blood and Bone Marrow Cancers (Hematologic Malignancies) and Bone Marrow Transplant
Directed by **Richard Jones** and **Richard Ambinder**

Brain Cancer Disease Group and Brain Tumor Specialty Center
Directed by **Matthias Holdhoff** and **John Laterra**

Colorectal Cancer Research Center of Excellence
Directed by **Nilofer Azad**

The Greenberg Bladder Cancer Institute
Directed by **David McConkey**

Liver Cancer Multidisciplinary Clinic
Directed by **Mark Yarchoan**

Melanoma and Skin Cancer Multidisciplinary Program
Directed by **Suzanne Topalian**, Bloomberg~Kimmel Professor of Cancer Immunotherapy, and **William Sharfman**, Mary Jo Rogers Professor of Cancer Immunology and Melanoma Research. Clinical co-directors are **Julie Lange** and **Elise Ng**.

Head and Neck Cancer Center
Directed by **Carole Fakhry**. Otolaryngology-Head and Neck Surgery is directed by **David Eisele**. The Head and Neck Cancer disease group is directed by **Tanguy Lim-Seiwert**, and **Harry Quon** co-directs the Head and Neck Cancer Multidisciplinary Clinic.

Prostate Cancer Multidisciplinary Clinics, Precision Medicine Center of Excellence for Prostate Cancer, and Prostate/ Genitourinary Cancer Program
Directed by **Sam Denmeade** and **Sean Lupold**. Clinical research is directed by **Channing Paller**. Co-leaders of the Multidisciplinary Clinic are **Eugene Shenderov**, **Christian Pavlovich**, and **Danny Song**, and co-leaders of the Multidisciplinary Clinic in the National Capital Region are **Curt Deville**, **Channing Paller**, and **Armine Smith**. **Mark Markowski** is the leader of genitorurinary medical oncology in the National Capital Region.

The Skip Viragh Center for Pancreas Cancer Clinical Research and Patient Care
Co-directed by **Elizabeth Jaffee**, the Dana and Albert “Cubby” Broccoli Professor of Oncology, and **Daniel Laheru**, Ian T. MacMillan Professor of Pancreatic Cancer Research.

Precision Medicine Center of Excellence for Pancreatic Cancer
Directed by **Lei Zheng**

Thoracic Cancer Center of Excellence and Precision Medicine Center of Excellence for Lung Cancer
The Thoracic Oncology Program is directed by **Julie Brahmer**, and the Thoracic Oncology Multidisciplinary Program is directed by **Russell Hales**. The Precision Medicine Center is directed by **Valsamo “Elsa” Anagnostou**, and **Joseph Murray**. The Esophageal Cancer Research Program is directed by **Vincent Lam**. **Stephen Greco** is clinical director of radiation oncology at Suburban Hospital. Surgeon **Stephen Broderick** directs the Cardiothoracic Residency program.

Under Armour Breast Health Innovation Center and Women’s Malignancies
Antonio Wolff is acting director. **Jean Wrigh**t is director of the radiation oncology breast cancer program.

Beating Pancreatic Cancer

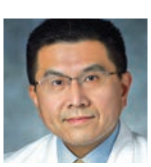

KATHLEEN

IN 1997, DARK urine and annoying itching all over her body, drove Kathleen, then 50, to see her doctor.

Her doctor suspected a gall stone. However, when routine surgery at a community hospital near her home to remove the gall bladder resulted in complications with her small intestine, pancreatic cancer was detected.


JAFFEE


DONEHOWER


ZHENG


CAMERON

The surgeon broke the devastating news to Kathleen's husband and 25- and 21-year-old daughters. He recommended Kathleen go to Johns Hopkins for surgery. The surgeon told the family that "Hopkins surgeons have the most expertise in doing this surgery," recalls Kathleen.

The next day, she was transferred by ambulance to Johns Hopkins and met with world-famous surgeon **John Cameron**. In a surgical procedure known as the Whipple, he removed Kathleen's pancreas, part of her stomach, and several lymph nodes.

The Whipple is the primary surgical treatment for pancreatic cancer, and Cameron pioneered significant improvements to the surgery. Under his direction, Johns Hopkins earned the reputation as the best in the world for pancreatic cancer surgery and for training the next generation of surgeons. These improvements made the complex surgery safe and dramatically reduced complications.

The lymph nodes are small glands that are part of the immune system and carry cells and fluid to other parts of the body. They provide a means for cancer cells to spread from the original tumor to other organs. Examination of the lymph nodes removed during Kathleen's surgery revealed that they contained cancer cells, meaning the cancer had begun to spread and would not be cured by surgery alone.

"I wasn't familiar with pancreatic cancer. I didn't know anyone who had it, so I really didn't understand how bad it was," says Kathleen. "I was shocked when I learned the statistics."

She still recalls the day she asked Cameron if the dismal pancreatic cancer survival rates she read about were true. He told her they were, but he also told her she could be the one to beat the odds.

She received chemotherapy to help mop up any remaining cancer cells. Gastrointestinal cancer expert **Ross Donehower** also told Kathleen about a clinical trial of a new cancer vaccine developed at the Kimmel Cancer by leading pancreatic cancer researcher **Elizabeth Jaffee**, co-director of the Skip Viragh Center for Pancreas Cancer Clinical Research and Patient Care.

"I wasn't familiar with pancreatic cancer. I didn't know anyone who had it, so I really didn't understand how bad it was. I was shocked when I learned the statistics."

"He said it might keep my cancer from coming back," says Kathleen. Given the statistics she read, she wanted to give it a try. She was the eighth patient to receive the vaccine.

The pancreatic cancer vaccine works by supercharging the immune system, causing cancer cells to seek out and kill cancer cells, including hunting down and cleaning up surviving cancer cells or newly appearing cells anywhere in the body. With few treatments for advanced pancreatic cancer, the vaccine attracted worldwide attention when it was developed in the early 2000s. The clinic received more than 60 inquiries each month from patients hoping to receive the vaccine. After Dr. Jaffee appeared on the *Dr. Oz* show in 2011, the clinic was flooded with more than 1,000 inquiries.

"We were the only Cancer Center at the time doing this kind of work," says **Lei Zheng**, who works with Jaffee on pancreatic cancer vaccines and other treatments for the cancer. He is also co-director of the Pancreatic Cancer Precision Medicine Center of Excellence, aimed at the quick translation of the latest research on vaccines and immunotherapy, molecularly targeted therapy, chemotherapy, radiation, and surgical techniques to patients.

After receiving two doses of the vaccine, Kathleen developed a condition called TTP that causes blood clots to form throughout the body. It was not caused by the vaccine, but it meant she would not be able to receive additional doses of the vaccine.

Remarkably, the two doses Kathleen received were enough, and 26 years later, she remains cancer free.

"I remember the doctors telling me I had the strongest immune response of anyone in the clinical trial," says Kathleen.

It is a complex process to activate the immune system to recognize pancreas cancer cells and simultaneously suppress mechanisms Kimmel Cancer Center researchers have revealed are co-opted by tumor cells to shut down the immune response. Jaffe, Zheng and the Skip Viragh Center team continue to study new approaches, including combining the vaccine with drug therapy or radiation therapy, and creating vaccines individualized to the unique molecular characteristics of a patient's cancer.

Today at 75, Kathleen is retired and enjoying her four grandchildren. She had one grandchild when she was diagnosed. "I didn't think I'd live to see her grow up," says Kathleen.


ONNERS

She started making bunnies, cladding them in fancy dresses. She thought it would be a way for her granddaughter to remember her. Now, they have are a lasting testament to her survival. Kathleen has made one for each of her grandchildren.

It wasn't an easy journey, and there have been a few scares along the way, such as a spot that showed up on a CT.

"They never amounted to anything," she says.

She is grateful to her doctor **Dan Laheru**, co-director of the Skip Viragh Center for being so thorough. After all these years, Kathleen still gets emotional when she thinks about her cancer battle. She has great respect for her doctors and nurses.

"Dr. Jaffee, Dr. Laheru, my nurse **Beth Onners**, I can't say enough about them," says Kathleen. "They are wonderful; top notch."

Scientist Becomes Patient

KIMMEL CANCER CENTER researcher **Christopher Umbricht** understands the power of translational research. In 2000, he found himself simultaneously a scientist working to understand an enzyme called telomerase and a patient, applying his research to thyroid cancer.


ZEIGER


UMBRICHT

Umbricht and cancer surgeon **Martha Zeiger** had been studying telomerase for several years as a potential biomarker for the detection of certain types of cancer, including breast cancer and thyroid cancer.

In a serendipitous twist of fate, Umbricht was among the early researchers to test telomerase in the lab, and he became the first patient at Johns Hopkins to have his tumor tested for this marker.

When a needle biopsy, removing a sampling of cells from a small lump on his neck, revealed a follicular thyroid tumor, he was shocked that his research was now becoming his personal reality.

The treatment of follicular thyroid tumors is a medical challenge. Unlike other tumors that display obvious signs of being either a cancer or a harmless benign tumor, follicular thyroid tumors are not so clear cut. The entire tumor must be removed surgically and examined under a microscope to determine if the tumor is cancer, and until recently, this was done by performing a complete removal of the thyroid gland, requiring lifelong treatment with oral medications to replace the natural hormone. "Without a sure way to know, we could not risk leaving the gland in when it might be cancerous," says Zeiger.

Yet, the majority of tumors — about 80% — are benign, and would not have required surgery if there was a nonsurgical way to distinguish cancer from noncancer.

If they could figure out a way to identify the cancerous tumors requiring surgery to remove the whole thyroid, they could spare 15,000 people each year unnecessarily invasive surgeries and the need for lifelong medication, she says.

The thyroid is a small, butterfly-shaped organ in the front of the neck that performs a mighty job. It produces hormones that are carried throughout the bloodstream to every cell in the body. All of a person's organs — the heart, brain, liver, kidneys and skin — require the right amount of thyroid hormone to function correctly. Body temperature, cholesterol levels, moods and memory are all affected by the thyroid hormone.

Umbricht was confident enough in their telomerase research that he wanted to use the biomarker to guide his treatment. Zeiger was not convinced.

Despite persuasive laboratory studies on human tumors, the findings had not been used to alter therapy. The use of telomerase as a tumor marker was still in the research phase, and she advised Umbricht to have the surgery.

The cells removed from Umbricht's tumor during the needle biopsy did not show signs of telomerase, indicating the tumor was benign.

Therefore, Umbricht opted for more limited surgery, removing just the thyroid lobe containing the tumor. Fortunately, the microscopic exam confirmed the absence of cancer tissue.

As the research advanced and technologies improved and they delved deeper into the research, as is often the case with cancer, it proved to be more complicated.

With their ongoing research, the initial success in using the telomerase enzyme to distinguish thyroid cancer from benign thyroid tumors revealed some problems. Their initial biomarker lacked the sensitivity (ability of a test to correctly find disease in the person tested) and specificity (ability of a test to correctly determine the person tested is disease-free) to be a viable cancer test.

The precision medicine goal of directing treatment to the patients who need it and away from those who could be safely spared surgery and lifelong medication remains an important area of research, however, and progress has been made.

Zeiger, Umbricht and collaborators have now shifted their focus to the role of easily detectable genetic mutations in telomerase genes as a more reliable biomarker, and one that seems to mark aggressive tumors that are most likely to spread to other parts of the body. They continue to study the biomarker in samples of follicular thyroid tumors removed during surgery as they work toward a test that could reliably guide therapy.

PIONEERING THE WHIPPLE

Surgeons, like **John Cameron**, have made significant improvements to the Whipple procedure, the primary surgical treatment for pancreatic cancer that occurs within the head of the gland (also called a pancreaticoduodenectomy). Today, our surgeons perform a high volume of these procedures and have lessened the complications during and after surgery.

Pancreatic surgery, once associated with a very high risk of surgically related death, has since dropped to 2% — when performed by an experienced surgeon — because of improvements made to the Whipple by Cameron and his trainees.

Cameron performed more than 2,000 Whipple procedures — more than anyone in the world — and trained a team of pancreatic surgeons to carry on his legacy.

TITANS OF PROSTATE CANCER

Urologist **Patrick Walsh** is perhaps the most famous and revered figure in the world of prostate cancer. For 30 years, he served as Director of the internationally renowned Brady Urologic Institute at Johns Hopkins. He transformed prostate surgery by developing an anatomical approach to remove the cancerous prostate without causing the life-changing side effects and taught the procedure to hundreds of urologists-in-training.

Forward thinking, Walsh compiled an extensive database of thousands of patients and followed them for 30 years, which **Donald Coffey** and others who trained with Coffey used to decipher some of the first insights into the basic biology of prostate cancer.

In June 2011, he performed the procedure he pioneered for the last time. It was his 4,569th prostatectomy.

Alan Partin, the Jakurski Director of the Brady Urologic Institute, from 2004-2022, passed away in 2023, but his impact on prostate and other urological cancers lives on. A noted physician-scientist and prostate surgeon,Partin developed a method to predict the prognosis of prostate cancer. He pursued science with creative vigor, cared for thousands of patients with kind expertise and led the urology department through strategic growth, broadening its sphere of influence while maintaining the depth of scientific understanding that continues to inform patient care.

Under Partin's leadership, the Brady Urological Institute doubled its research space and enjoyed significant expansion with projects, such as the world-renowned Greenberg Bladder Cancer Institute and new clinical space at Green Spring Station Pavilion III.

He is known for developing the Partin Tables, which are used for predicting the prognosis for prostate cancer, and for his work developing several innovative tests to identify and track prostate cancer, including the Prostate Health Index.

Throughout his 40-year career as a researcher, a clinician and a leader, Partin was consistently at the heart of discovery and innovation in the field of urology, always keeping a singular focus on improving outcomes for our patients. He embodied the best of Johns Hopkins.

He earned his doctorate in pharmacology and molecular sciences in 1988 and his M.D. 1989 at the Johns Hopkins University School of Medicine. After completing his residency at Johns Hopkins, he joined The Brady Urological Institute as an associate professor in 1995.

In December 2022, the Alan W. Partin, M.D., Ph.D., Professorship in Urology was established to support research to develop diagnostic tools, treatments and cures for prostate cancer.

In more than 50 years at Johns Hopkins, **Donald Coffey**, the Catherine Iola and J. Smith Michael Distinguished Professor of Urology and professor of oncology, pharmacology and molecular sciences, and pathology, racked up a long list of accomplishments. Many of his accolades are as unconventional as the man. He served as acting chair of the Department of Pharmacology without every taking a course in pharmacology. With no medical degree, he helped found the Cancer Center in 1973 with its first director **Albert Owens**, and then ran it in 1987. He described himself as one of academia's worst students, but he was an astute learner and an even better teacher and was one of the foremost experts in prostate cancer.

COFFEY

The early research of Coffey was, in many ways, the bedrock on which modern genetic and epigenetic discoveries at Johns Hopkins were built. In 1974, he turned the research world upside down, challenging the popular thought on how DNA was copied. The prevailing thought of the time was that there was no single place in the cell where DNA was copied. Coffey disagreed. He believed the core of the nucleus was where DNA was copied, and the tape-like strands — a yard long — were coiled tightly inside the cell nucleus.

"The nucleus has a skeleton to it. That's the nuclear matrix," explained Coffey. He believed, however, that people would have to see it to believe it.

"**Ken Pienta** and I went to Sears and bought a jigsaw, and we built an award-winning scaled model, 175 feet long, of a relaxed single loop of DNA magnified 25 million times," recalled Coffey. Another model, this one just four feet long, was constructed to illustrate the super-coiled loops of DNA.

Coffey explained that cancer was like the body's genetic tape playing the wrong song at the wrong time. "The tape is all mixed up and contains errors," he said.

Understanding what is on the tape and how it is played in cancer has been one of the greatest scientific contributions of Johns Hopkins and its Kimmel Cancer Center. He also planted the seeds for the future multidisciplinary clinics. He believed that much could be learned if people from different specialties could just get together and talk about a problem.

A consummate teacher, Coffey continued to use models, Slinkys, soap bubbles, soda cans, and more to train the next generation of cancer researchers, which included **Ted DeWeese**, Interim Dean of the Johns Hopkins School of Medicine, **William Nelson**, Kimmel Cancer Center Director, **Bert Vogelstein**, Co-Director of the Ludwig Center for Cancer Genetics and Molecular Therapeutics, and **Drew Pardoll**, Director of the Bloomberg~Kimmel Institute for Cancer Immunotherapy.

The classroom and the laboratory never closed for Coffey. In the hallways of the Brady and the Kimmel Cancer Center, in his office over high tea, or in a conference room, he could be found fostering collaborations and inspiring new ideas about cancer.

Coffey trained some of the greatest minds in the Kimmel Cancer Center, and although he passed in 2017, his lessons are timeless:

Don't assume anything you can't prove.

The experiment that doesn't come out the way you think it should is the only experiment that is really going to teach you something new.

If you find something to be true, what does it imply? *Often we don't need more experiments we need more critical thinking about the results.*

Generate more than one concept to explain your data, then give all the possibilities your equal attention and effort. *Your pet idea will usually turn out to be just that.*

When discoveries are made give everyone credit. *You were probably not the first one to study the problem, nor will you be the last.*

MORE TITANS AND PIONEERS

The Kimmel Cancer Center also recognizes these Cancer Center titans and pioneers:
Prostate cancer: **Michael Carducci, Mario Eisenberger**, **John Isaacs**, **William Isaacs**, **Ken Pienta**, and **Hugh Jewett**; Cancer pathology: **Ralph Hruban** and **Robert Kurman**; Cancer research: **Scott Kaufman** and **Strat May**; Viral oncology: **John Nicholas** and **Prashant Desai**; Head and Neck Cancer: **Wayne Koch** and **Joseph Califano**; Cancer surgery: **John Niederhuber** and **Rick Schulick**; Solid tumors: **Skip Trump**.

CANCER RESEARCH | ADVANCES

A HISTORY OF PROGRESS AGAINST PROSTATE CANCER

Performed the first prostatectomy in 1904 and later pioneered the atomical nerve sparing approach

Developed some of the first therapeutic approaches and clinical models for prostate cancer, including the earliest form of brachytherapy, and were the first to culture human prostate cancer cells to study therapeutic targets

Developed the first animal models to characterize the properties and types of prostate cancer

Discovered the first human gene mutation in prostate cancer

Deciphered the mechanisms for prostate cancer metastasis

Provided the first description of the basic cellular and molecular properties of prostate cancer

Were the first to describe the importance of stem cells in prostate cancer

Deciphered how prostate cancer growth is regulated

Defined hereditary prostate cancer

Performed the first DNA methylation studies in prostate cancer

Developed an animal model of prostate inflammation and defined proliferative inflammatory atrophy, a new model for what causes prostate cancer

Pioneered quantitative pathology to refine staging and prognostic markers

Developed the Partin Tables, Pound Tables, and Han Tables to predict localized cancers, relapse time, metastasis, and survival

Used PSA velocity to define lethal types of prostate cancer

Developed and clinically tested the first prostate specific adenovirus to treat recurrent and metastatic prostate cancer

Performed the first protein analysis of normal prostate and prostate cancer

Developed new biomarker tests for prostate cancer

Led the work in robotics for prostate cancer treatment

Pioneered tumor immunology studies and developed GVAX, the first therapeutic vaccine for prostate cancer

Identified new drug targets, PSA negative activated pro drugs and other agents

NEWS THAT BROKE IN THE 2000s

2001
On September 14, 2001, Kimmel Cancer Center patients, faculty and staff members joined together in a healing service following the tragic terrorist attacks of September 11, 2001.

2002
Baltimore Magazine's "Best Doctors" issue included Kimmel Cancer Center oncologists **Martin Abeloff**, **Nancy Davidson**, **Ross Donehower**, **Mario Eisenberger**, **David Ettinger**, **Stuart Grossman** and **Georgia Vogelsang**.

2003
Scott Kern links three genes associated with a rare disease known as Fanconi's anemia to a subset of pancreatic cancers.

Joel Shaper was selected to serve on the National Institutes of Health Pathobiochemistry Study Section.

2004
Sauk Sharkis finds that bone marrow stems cells exposed to damaged liver tissue converted into healthy liver cells and helped repair the damaged organ.

Angelo De Marzo and **Alan Meeker** find that abnormal telomeres, the protective end caps on chromosomes, play a causal role in cancer development.

2006
Saraswati Sukumar uses a tiny catheter inserted through the nipple to deliver anticancer drugs directly into the breast ducts.

Deborah Armstrong revives a 50-year-old method for delivering chemotherapy directly into the abdomen for patients with ovarian cancer.

Akilesh Pandy and colleagues at the Institute for Bioinformatics in Bangalore, India, create the Human Protein Reference Database of more than 25,000 human protein-to-protein interactions.

Victor Velculsecu reports that the PIK3CA gene is one of the two most highly mutated oncogenes (tumor promoting gene) discovered in human tumors.

William Nelson and **Angelo De Marzo** find that PhIP, a compound found in meats cooked at very high temperatures, such as open flames, could be linked to prostate precancers.

Paula Pitha-Rowe identifies a gene, ISG15, as an inhibitor of a cellular pathway used by HIV-1, the AIDS causing human immunodeficiency virus.

2007
Chi Dang finds that the role of antioxidants may be to destabilize a tumor's ability to grow in oxygen-starved conditions.

Rhoda Alani, identifies a gene expression pattern that could help pinpoint deadly melanoma skin cancers.

Allison Klein, develops PancPRO, a risk calculator for pancreatic cancer.

2009
For the 19th consecutive year, the Johns Hopkins Hospital earns the *U.S. News and World Report*'s top spot in its annual rankings of America's hospitals. The Kimmel Cancer Center ranks among the top three cancer centers in the nation.

G. Steven Bova works from the autopsies of 33 men who died of prostate cancer, examining 150,000 slides and 30,000 blocks of tissue and traces the origin of each person's cancer to a single cell source.

Charles Rudin finds that lung cancers in never smokers have more mutations of the EFGR gene, making these patients candidates for therapies that block EGFR signaling.

The Kimmel Cancer Center's Next Generation Sequencing Lab opens under the direction of **Vasan Yegnasubramanian** and **Sarah Wheelan**, allowing researchers to see inside the cancer cell in ways never before possible and speeding the pace of discovery.

Carol Greider wins the Nobel Prize in Physiology or Medicine for her discovery of telomerase, an enzyme that restores telomeres, protective caps that protect the ends of chromosomes. The connection of telomeres and telomerase to cancer development is a major area of cancer research.